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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
07/967,267	10/27/92	COOK	P ISIS-0710

EXAMINER

12M1/0722

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KUNZ, G	PAPER NUMBER
ART UNIT	

1211

28

DATE MAILED: 07/22/97

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 3-31-97

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 9-10 and 15-27 is/are pending in the application.  
Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 9-10 and 15-27 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

08/967,267

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Applicant's Request for Reconsideration filed 3-31-97 has been received and entered into the record.

Any 35 USC statutes not cited in this Office action can be found cited in full in a previous Office action.

Claims 9 - 10 and 15 - 27 are pending in the case.

Claims 9 - 10 and 15 - 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1 - 8, 62 - 63, and 69 - 72 of copending application SN 08/373,298 for the reasons already of record on pages 5 - 6 of the Office action mailed 5-16-96. Applicant's request to defer this rejection until all of the other outstanding rejections have been overcome is acknowledged.

The rejection of claims 9 - 10 and 15 - 27 under 35 USC 112, first paragraph, for failing to provide an enabling specification has been withdrawn in view of applicant's persuasive arguments that some inoperable and some less than optimal species within a genus claim does not obviate the enablement of the claim as a whole.

The rejection of claims 9, 10, and 15 - 27 under 35 USC 103 as being unpatentable over WO 90/08156 (Teuole) in view of Kikuchi has been withdrawn in view of applicant's arguments that clarifies the teachings of Teuole wherein the moiety is attached to the 2'-carbon of the nucleoside rather than to an oxygen already bound to said 2'-carbon.

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Claims 9 - 10, and 15 - 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

✓ Claims 17 - 19 are rendered vague and indefinite because there is no antecedent basis for variable "n" being zero in claim 9. Claim 9 specifically requires that the variable "n" be 1 to about 6, but not zero.

✓ Claims 9, 10, 20 - 22, and 26 - 27 are rendered vague and indefinite because of the use of "about six" in defining a variable which must be an integer. All other claims stand rejected as depending from a rejected claim.

✓ Claims 22 and 25 are rejected because they are substantial duplicates of one another. Note that the definitions of R1 are identical and that "n" is already defined as "1 to about 6" in independent claim 9. This duplication has probably occurred because claim 25 depends from claim 9 rather than claim 10.

Claims 9, 15 - 22, and 25 - 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohtsuka et al.

The claims are directed to 2'-O-substituted derivatives of guanosine and 2'-aminoadenosine and oligonucleotides containing one or more of these nucleosides.

Ohtsuka et al. discloses 2'-O-substituted nucleosides (claim 11 - 15) and oligonucleotides containing said nucleoside derivatives (claims 1 - 10 and 16 - 17). Claim 4 cites ethyl as the 2'-O-

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substituent. Claim 7 cites methyl as the 2'-O-substituent. Claim 5 cites propyl as the 2'-O-substituent. Instant claim 9 still encompasses 2'-O-methyl, 2'-O-ethyl, and 2'-O-propyl, and 2'-O-allyl because of the phrase "a group that enhances the pharmacodynamics properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides". Therefore, Ohtsuka et al. not only discloses any nucleoside 2'-O-substituent generally and the corresponding oligonucleotide, but specifically claims lower alkyl (methyl, ethyl, and propyl) as the preferred substituents. Therefore, the person of ordinary skill in the art at the time of the invention would have found it obvious to have substituted methyl, ethyl, or propyl groups at the 2'-O-position of a nucleoside for the purpose of conferring nuclease resistance upon the corresponding oligonucleotide. Thus, the claimed invention is prima facie obvious in the absence of clear and convincing evidence to the contrary.

Claims 10, 23 - 24, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohtsuka et al. in view of Kikuchi. The claims are directed to 2-aminoadenosine-2'-O-substituted derivatives and the corresponding oligonucleotides containing them.

The teachings of Ohtsuka et al. are set forth above. The only significant difference between these claims and the above claims is that 2-aminoadenosine is the purine nucleoside instead of guanosine. However, Kikuchi et al. teaches the use of 2-aminoadenosine in place of adenosine in oligonucleotides because this substitution gives increased binding affinity between complementary polynucleotides. Therefore, the person of ordinary skill in the art would have also found it obvious to have modified the 2-aminoadenosine taught by Kikuchi et al. by substituting

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methyl, ethyl, or propyl, at the 2'-O-position for the purpose of producing a nucleoside with increased hybridization affinity and with nuclease resistance. The art of biochemistry further recognizes the common substitution of fluorinated alkyl derivatives in place of an unsubstituted alkyl group because these two groups possess similar size and reactivity.

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ohtsuka et al. in view of Kikuchi et al. and Iribarren et al. (PNAS 87: 7747 - 7751, 1990).

The claim is directed to 2'-O-allyl derivatives of 2-aminoadenosine. The teachings of Ohtsuka et al. and Kikuchi et al. are set forth above. The only deficiency in these first two references is the lack of a specific teaching for nucleoside 2'-O-allyl derivatives. However, Iribarren et al. does disclose 2'-O-allyl nucleosides and oligonucleotides containing same for the purpose of increasing hybridization affinity with nuclease resistance. Therefore, this invention is also prima facie obvious in the absence of clear and convincing evidence to the contrary.

While the above obviousness rejections are new grounds for rejection, applicant's key argument to the previous obviousness rejection will be addressed. The applicant argues that the obviousness rejections, especially with respect to guanosine, should be withdrawn because the artisan would not have had a reasonable expectation of being able to prepare these more difficult nucleoside 2'-O-substituted derivatives. This argument has been fully considered but is not deemed persuasive. Ohtsuka et al. discloses specifically 2'-O-methyl-N2-isobutyrylguanosine in column 4, line 32. This 2'-O-substituted guanosine was prepared with

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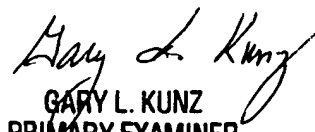
diazomethane (column 4, lines 26 - 29). Similar diazo-reagents could have been used to prepare other 2'-O-substituted derivatives of guanosine even. While this might not be an efficient or convenient synthesis, the law does not require either efficiency or convenience for obviousness--only a reasonable expectation of success. The Ohtsuka et al. references establishes that there was precisely such a reasonable expectation of success in preparing a variety of 2'-O-substituents.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz, whose telephone number is (703) 308-4623. The examiner can normally be reached on Tuesday through Friday from 6:30 AM to 4:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Kight, can be reached on (703) 308-0204. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Gary L. Kunz, Ph.D.  
July 18, 1997

  
GARY L. KUNZ  
PRIMARY EXAMINER  
GROUP 1200